Head and neck cancer is a major public health problem. In the United States alone, approximately 43,000 new cases of head and neck cancer will be diagnosed and 11,000 persons will die of the disease in 1993 (1, 2). Worldwide, over 500,000 new cases of this cancer occur yearly, and the incidence is rising. Furthermore, despite intensive efforts in primary prevention, screening, and therapy, long-term survival rates have not improved substantially since the 1960s. Standard treatment for head and neck cancers consists of surgery, radiotherapy, or both, and is met with mixed results. Standard treatment is frequently initially successful in early stage disease, but even in early stage disease, initial success is tempered by the potential for long-term development of deadly SPT. Against advanced disease, standard therapy is less successful, generally producing cure rates under 50%. Standard local therapy of surgery and radiotherapy, even when successful, can cause significant functional and cosmetic deformities, leading to a tremendous loss of quality of life. Despite improvements in reconstructive surgery and rehabilitation, patients who require total laryngectomy, glossectomy, or composite resection for curative therapy suffer major lifelong disabilities (1, 2). Furthermore, the treatment advances that extend these patients’ lives are undermined by the development of SPT (3, 4). The crucial therapeutic issues of severe morbidity and the significant rate of development of SPT in “cured” head and neck cancer patients are responsible for the emerging importance of two new approaches to these diseases, organ preservation and chemoprevention.

Advances in Organ Preservation: Laryngeal Cancer

Laryngeal cancer is the most common head and neck cancer, representing roughly 30% of all cases in the United States. The standard treatment for locally advanced laryngeal cancer is total laryngectomy and postoperative radiotherapy (1, 2). Laryngectomy may be associated with impairments in smell, taste, and swallowing ability, but unquestionably, the major problem relates to the loss of natural speech. Laryngeal cancer patients are often willing to make tradeoffs between quality and quantity of life in order to preserve their larynx (5).

Although advances in surgical techniques have had some impact on morbidity, primary chemotherapy for organ preservation is being investigated as an alternative to the surgical component of current standard therapy (1, 2).

Historical Perspective. The first primary chemotherapy approaches in locally advanced head and neck cancer, begun in the early 1970s, involved single-agent methotrexate. Survival after methotrexate followed by definitive local therapy was no different than that after standard local therapy, nor did methotrexate increase morbidity. This lack of increased morbidity highlighted the feasibility of this approach and encouraged investigators to use cisplatin in this setting when the high level of activity of this agent became known a little later in the 1970s (6).

Investigators were excited by the striking early response rates of locally advanced head and neck disease to combined cisplatin and bleomycin, 70–80% overall and 20–30% complete (1, 2, 6, 7). The potential advantages of this primary chemotherapy approach were evident; dramatic tumor shrinkage would greatly enhance surgical and radiotherapy cure rates and could achieve an important adjuvant effect by eradicating micrometastatic disease, substantially improving local-regional control and reducing the incidence of distant metastases. No one questioned that primary cisplatin-based chemotherapy would improve survival, only how great the improvement would be.

A definitive phase III trial of primary cisplatin-bleomycin was begun in 1978 (8). This three-arm, multicenter United States trial involving 462 patients was the first to capture widespread multidisciplinary enthusiasm for primary chemotherapy in the head and neck. The trial included locally advanced resectable cancer of multiple head and neck sites and compared standard surgery-radiotherapy and two experimental therapies, primary chemotherapy (cisplatin-bleomycin) with and without maintenance cisplatin. Although begun with the highest expectations, this trial culminated in 1982 by demonstrating that these chemotherapy regimens did not increase the rates of disease-free or overall survival over those of the standard surgery-radiotherapy regimen.

In 1983, the National Cancer Institute convened a conference of investigators to determine whether there were any positive indications from the generally disappointing results of these primary chemotherapy trials. One of the most positive findings from all the data was that the minority of patients who achieved a major response and then refused subsequent surgery had survival rates similar to those of patients who received the planned surgery after chemotherapy. It was this subset analysis that provided the direction for continuing investigation and led to organ preservation becoming a major focus of primary chemotherapy strategies in head and neck cancer. The major goal of organ preservation studies with primary chemotherapy is to eliminate the need for surgery, thereby preventing loss of organ function or severe disfigurement without compromising survival.

The first studies specifically dealing with the role of primary chemotherapy for organ preservation were reported by Jacobs et al. and Hong et al. in the mid 1980s. Jacobs et al. (9) treated 30 patients with cancers of several head and neck sites with chemotherapy. The 12 patients who achieved histological complete responses then received radiotherapy only; the 18 patients who did not achieve complete...
responses were treated with standard surgery and radiotherapy. At 2 years, the respective disease-free and overall survival rates for all 30 patients were 52 and 53%, while the survival rates for the 12 patients who achieved histological complete responses and avoided surgery were 60 and 70%, respectively. This study was small and nonrandomized but did suggest that surgery could be avoided without compromising survival in patients treated with primary chemotherapy who achieved histological complete responses.

The study by Hong et al. (10) was the first to focus on primary chemotherapy and organ preservation specifically with regard to laryngeal cancer and was among the first to report patterns of response with sequential chemotherapy-radiotherapy. The 46 patients analyzed were treated on three primary chemotherapy protocols; reasons for not having surgery included patient refusal, doctor refusal, and medical contraindications. The report differed from the study by Jacobs et al. in that all patients who received sequential chemotherapy-radiotherapy were analyzed, regardless of chemotherapy response. Hong documented that chemotherapy response predicted radiotherapy response. Of 28 patients who achieved a partial response to chemotherapy, 22 (79%) achieved a complete response after radiotherapy. In contrast, of 11 patients who achieved less than a partial response to primary chemotherapy, only 2 (18%) achieved a complete response after radiotherapy ($P = 0.0002$). Hong et al. focused on the potential great benefit, in terms of both morbidity and quality of life, of this approach for the 20 patients in the study with laryngeal or hypopharyngeal cancer who would otherwise have required total laryngectomy. Of these 20 patients, 13 achieved partial responses after chemotherapy, and all 13 partial responders achieved a complete response after radiotherapy. The overall survival rate was similar to that reported with standard laryngectomy. This report extended the findings of Jacobs et al., which applied only to histological complete responses, and suggested the potential of this organ preservation strategy for all chemotherapy responders. The observations of Hong et al. led directly to the design of the Veterans Affairs (VA) trial, which focused on patients who would require laryngectomy for cure. Concurrently with the studies of Hong et al., Jacobs et al., and others, investigators at Wayne State University developed a regimen combining cisplatin and 5-fluorouracil. This appeared to be superior to other cisplatin-based regimens, producing complete response rates as high as 54% after three courses in locally advanced disease (1, 2, 11).

Even though none of the primary chemotherapy trials had prolonged survival, they did demonstrate the feasibility of this approach and that chemotherapy response predicts radiotherapy response. In addition, they suggested that this approach might reduce treatment morbidity. These silver linings of an otherwise negative collection of data led to a highly significant multicenter trial specifically designed for organ preservation.

The Veterans Affairs Laryngeal Cancer Study Group Trial. In the early 1980s, the VA Laryngeal Cancer Study Group designed a prospective randomized phase III trial to compare survival rates in patients with resectable stage III or IV laryngeal cancer treated with sequential chemotherapy and radiotherapy, or with a standard treatment of laryngectomy and postoperative radiotherapy (12). The hypothesis for this study was that combined chemotherapy-radiotherapy could achieve equivalent survival rates with better quality of life (larynx preservation and function) than total laryngectomy and radiotherapy for patients with advanced laryngeal cancer.

Laryngeal cancer was the primary site selected for the study because of the very debilitating functional and psychosocial effects of the loss of natural speech (5). In addition, many laryngeal cancer patients were reluctant to undergo radical surgery and were already choosing radiation alone with surgical salvage. Therefore, the timing for a definitive phase III study seemed appropriate. This is the largest study yet to be performed of a single site within the head and neck.

This trial compared treatment with induction chemotherapy (cisplatin, 100 mg/m²/day, and 5-fluorouracil, 1 g/m²/day for 5 days, for three cycles) plus sequential definitive radiotherapy (66–76 Gy to the primary tumor site) to treatment with standard surgery and postoperative radiotherapy (50–60 Gy). Patients randomized to receive induction chemotherapy underwent response assessment after two cycles of cisplatin-5-fluorouracil. Those achieving at least a partial response received a third cycle, followed by definitive radiotherapy, followed by direct laryngoscopy and primary tumor site biopsy to determine histological response. In this group, surgery was reserved for later salvage of persistent or recurrent disease. Nonresponders to induction chemotherapy (those who had a tumor response of <50%) underwent immediate surgery followed by radiotherapy (Fig. 1).

The specific design feature of immediate surgical salvage after failure of two cycles of chemotherapy was based on three key issues. (a) This approach minimized the delay in performing surgery and therefore improved chances for survival, (b) radiotherapy is frequently less successful after chemotherapy failure, (c) morbidity is often increased after full dose chemotherapy and radiotherapy and may prevent definitive resection.

Between 1985 and 1989, a total of 332 patients from 14 VA hospitals were enrolled, and equal numbers were assigned to the surgery-radiotherapy arm and chemotherapy-radiotherapy arm. The two arms were balanced with regard to major prognostic factors, including stage (III, IV), TN subset, laryngeal subsite, vocal cord fixation, thyroid cartilage invasion, and performance status. The quality of the study and compliance rate were high; only 2% of randomized patients were lost to follow-up. Currently, the median follow-up is 60 months (range, 12–90 months).

After two cycles of induction chemotherapy, 85% of patients achieved a major response at the primary tumor site (31% complete response). After three cycles of chemotherapy, the overall response rate was 98% (49% complete), and 64% of patients had a pathological complete response (i.e., a histologically negative biopsy at the primary tumor site).

The estimated 3-year survival rates were 56% (48–64%) for surgery-radiotherapy and 53% (45–61%) for chemotherapy-radiotherapy (Fig. 2). There were no significant differences in survival based on subsite within the larynx (glottic or supraglottic), stage (III or IV), or response to chemotherapy (13). The data indicate that the short delay in definitive surgery in the chemotherapy nonresponders was not detrimental. The duration of survival of the 18% of patients who underwent salvage laryngectomy immediately after one or two cycles of chemotherapy (because of either a poor response or an inability to tolerate chemotherapy) was similar to that in the group that received initial surgery-radiotherapy. Although early surgery can effectively salvage local disease in most chemotherapy nonresponders, recurrent disease is often unresectable in patients who have been treated with...
chemotherapy-radiotherapy, and these patients have higher surgical complication rates (e.g., major wound infections) than patients who have surgery after chemotherapy alone.

Sixty-two percent (103 of 166) of patients in the chemotherapy arm were able to preserve their larynxes. Furthermore, 66%, or 52 of the 79 surviving chemotherapy-radiotherapy patients, are still able to communicate using their natural speech. The function (i.e., speech and swallowing) of the retained larynx in these patients is being systematically studied by rigorous speech assessments (speech intelligibility, acceptability, reading rate, vowel duration, and general communication profile). Initial evaluation of patients up to 2 years after therapy indicated that the chemotherapy-radiotherapy group had significantly better speech than the artificial speech achieved in the surgery-radiotherapy group. In addition, patients in the chemotherapy-radiotherapy arm experienced less difficulty swallowing. Chemotherapy-associated toxic effects were acceptable and did not interfere with subsequent radiotherapy or surgery.

Given these recent survival and larynx preservation rates, selected patients with locally advanced laryngeal cancer now have the option of preserving their voice box without risking shorter survival. Significant differences between study arms were evident in the patterns of first treatment failure: primary site recurrence was more frequent in the chemotherapy-radiotherapy arm and distant metastasis was more frequent in the surgery-radiotherapy group. There were no significant differences in regional node recurrence rates between the two study arms. The significant difference in patterns of failure disappeared over time when all sites of tumor recurrence (first and subsequent sites) were considered (i.e., many chemotherapy-radiotherapy patients who had first relapsed locally were effectively salvaged surgically but later developed distant metastases). The differences in first site failure patterns are explained by the fact that the primary local site (the larynx) was removed in the surgery-radiotherapy group, thereby greatly reducing local recurrence rates in this group. Ultimately, therefore, the overall rates of distant metastases were the same in the two arms. The time to first developing distant metastases, which would indicate whether chemotherapy delayed the development of distant metastases, has not been analyzed.

Two critical components of organ preservation trials involving primary chemotherapy-radiotherapy are careful patient surveillance after chemotherapy and early surgical salvage for nonresponders to initial chemotherapy. This successful application of primary chemotherapyradiotherapy in preservation of the larynx opens new avenues for application of this strategy in patients with locally advanced cancer of other head and neck primary sites.

Although equivalent to that of surgery-radiotherapy, the 3-year survival rate of approximately 50% for patients who received chemotherapyradiotherapy is unacceptable. Alternative strategies that will preserve organ function and prolong survival need to be investigated. Strategies now being tried include concomitant chemotherapy-radiotherapy, altered radiotherapy fractionation schedules, early planned neck dissection (in the absence of response to chemotherapy for advanced nodal disease) for enhanced local-regional control, and intensive multiagent chemotherapy for the treatment of distant micrometastases.

An unresolved issue raised by the positive results of the phase III VA trial is whether the rate of laryngeal preservation after primary chemotherapy-radiotherapy is superior to that after primary radiotherapy alone. A primary radiotherapy arm was not included in the VA trial; this therapy was not considered standard or ethical because, in historical comparisons with surgery-radiotherapy studies, it appeared to have yielded lower survival rates. No phase III trial has compared primary radiotherapy (with surgical salvage) with standard surgeryradiotherapy, although both approaches have been available for decades. Although several single-arm trials of primary radiotherapy in selected patients with T\(_3\)N\(_0\) disease have reported 5-year survival rates equivalent to those of surgery-radiotherapy (1, 2), many studies strongly suggest that primary radiotherapy is less effective than primary surgery for the more advanced disease which characterized the VA study population; the approximately one-half with stage IV disease, 25% with T\(_4\) lesions, and 50% with nodal disease (many with advanced N\(_2\,3\) disease) would apparently have been unlikely to do well with primary radiotherapy alone.

Early phase III results from other chemotherapy-radiotherapy studies, including a large French study, appear to confirm the VA trial and suggest a role for this approach in other head and neck sites (14).

Fifteen years after induction chemotherapy was introduced into the treatment of head and neck cancer, an intergroup study was developed based on the findings of the VA Laryngeal Trial. This will be the first time in history that a trial has been developed for advanced laryngeal cancer patients which does not use initial laryngectomy as standard treatment. The new multicenter phase III three-arm trial includes the experimental sequential chemotherapy-radiotherapy arm from the VA trial, a concomitant chemotherapy-radiotherapy arm, and a third radiotherapy-only control arm, which will resolve the radiotherapy versus chemotherapy-radiotherapy issue by direct comparison (Fig. 3). To accommodate the radiotherapy arm, this study differs from the VA trial in several key areas, including patient eligibility (excludes T\(_4\)) and treatment plan (patients with nodal disease have elective neck dissection after completing primary therapy).

**Advances in Chemoprevention**

Chemoprevention is a relatively new approach for controlling cancer of the UADT. Chemoprevention is defined as the use of specific natural or synthetic chemicals to reverse or suppress premalignant carcinogenic progression to invasive malignancy (15–18).

Reviewed in this section are the biological concepts of chemoprevention (multistep and field carcinogenesis and mechanisms of reti-
noid action) and the record of randomized chemoprevention trials in the head and neck.

**Biology**

Understanding the biology of carcinogenesis is crucial to the development of effective chemoprevention. Two basic concepts supporting chemoprevention are the multistep nature of carcinogenesis and the diffuse field-wide carcinogenic process.

**Multistep Carcinogenesis.** Epithelial cancer appears to develop in a recognizable and predictable series of steps. Epithelial carcinogenesis is conceptually divided into three phases: initiation; promotion; and progression. Evidence of multistep carcinogenesis is well documented in many animal models. This process has also been inferred from human studies identifying clinical-histological premalignant lesions (e.g., leukoplakia, metaplasia, and dysplasia) associated with malignant transformation rates of up to 30–40% (19, 20).

This concept has recently been analyzed in molecular studies which have identified a continuum of accumulated specific genomic alterations that take place in the clonal evolution of epithelial neoplasms. The molecular genetic basis of the multistep process in humans is most apparent in the progression of adenoma-carcinoma in the colon. This progression follows a sequence of events from ras mutation through allelic losses on chromosomes 5q, 17p, and 18q, each event, or step, followed by clonal expansion (21). Multiple genetic events in other epithelial sites have been identified and are beginning to be sequenced. In the UADT, numerical (e.g., polysomy of 7 and 17) and structural (e.g., deletions of 3p and 18q) chromosome alterations have been detected in various histological stages of UADT carcinogenesis, including in “benign” epithelium adjacent to tumor (1, 2, 22). Specific molecular genetic alterations detected in premalignant UADT lesions include mutations of p53, reduced expression of RAR-β, and increased expression of c-erbB1, TGF-α, and c-myc (4, 23–27). Mutations of Ras and amplification of int-2, hst-1, and bcl-1 have currently been identified only in UADT cancers (1, 2).

**Field Carcinogenesis.** The seminal concept of field carcinogenesis was proposed by Slaughter et al. (28) in 1953. This concept proposes that multiple neoplastic lesions of independent origin occurring within an epithelial field can result from repeated exposure to a single carcinogen. Patients with cancer of the head and neck or lung, or who are at high risk of developing these cancers, most commonly have a history of exposure to cigarette smoke and are likely to have multiple clinically and histologically evident premalignant lesions within the aerodigestive tract (29). According to the field carcinogenesis theory, primary tumors and related SPT result from progression of commonly initiated, although genetically different, premalignant lesions.

Recent molecular genetic studies of histologically normal and premalignant epithelium from high-risk subjects and of malignant aerodigestive tract epithelia strongly support the field carcinogenesis concept. These studies suggest that multiple, genetically distinct lesions occur throughout the aerodigestive tracts of high-risk subjects and cancer patients. Studies of histologically normal and premalignant epithelia of the UADT and lungs of high-risk subjects detect multiple genetic abnormalities throughout these epithelial fields, including p53 mutations, 3p deletions, and aneuploidy, which are inferred to be early steps in the carcinogenic progression toward malignancy (22, 30–32).

The field carcinogenesis concept suggests that separate primary cancers that develop in a tissue region exposed to the same carcinogens would arise as independent clones with similar but unique molecular genetic alterations. Chung et al. (33) analyzed p53 mutations in 31 patients with primary head and neck cancers and related SPT by using single-strand conformation polymorphism. p53 was selected as the molecular probe for this study because mutations of this gene are known to be critical and common events in head and neck and other epithelial cancers (30, 31, 34–36). Twenty-one patients were found to have at least one p53 mutation, and in all cases the mutation was discordant. Mutations were found in only one of the primary tumors in 16 patients; of the 5 patients in whom mutations were found in both primaries, 4 had mutations in different exons within the p53 gene, and 1 had mutations in different codons of the same exon by polymerase chain reaction sequence analysis. The class of p53-base mutations (transitions) was the same in more than 70% of these primary tumors and related SPT. These class-related but distinct mutations of p53 in primary tumors and SPT provide strong molecular support for field carcinogenesis.

Neoplastic initiation by a common carcinogen is suggested by the high rate of mutations of p53 and by the similarity in the class of mutations. However, the discordant nature of the mutations indicates that SPT may arise as independent genetic events. These and other genetic and chromosomal alterations reveal that aerodigestive tract epithelia of high-risk subjects and cancer patients contain generalized and dynamic genetic instability which is associated with profound phenotypic alterations (22, 30–32, 37, 38).

Slaughter et al. based the field carcinogenesis concept on their study of surgical specimens of tissue surrounding oral tumors. The profound histological changes that occurred in this surrounding tissue ranged from mild hyperplasia to severe dysplasia and invasive cancer. Slaughter et al. reported that these changes occurred over a wide area which included clinically normal-appearing tissue.

This work, done over 40 years ago, laid the foundations for the technologically advanced molecular studies of field carcinogenic effects that we and others are currently conducting (22, 25, 30, 31, 38). As did Slaughter et al., we have examined surgical specimens of tissues surrounding head and neck tumors in addition to specimens of the tumors themselves, and we have observed many genotypic and phenotypic changes in these tissues.

The new methods allow us to pursue the subtletest molecular signs of field carcinogenesis not only in histologically abnormal tissues but also in histologically normal epithelia within the high-risk field. The markers we have studied to date are polypsomes of chromosones 7 and 17, mutations of p53, nuclear RAR, epidermal growth factor receptor, and proliferating cell nuclear antigen (22, 25, 37). Changes in these molecular and cellular markers are being compared with the histological yardstick of carcinogenic changes. Except for RAR, all the markers mentioned above change in direct relationship with histological stage; RAR-β changes inversely.

These results support the concept that cancers of the UADT are associated with field carcinogenesis and develop in a multistep process. Current work is attempting to correlate specific genetic events (e.g., gene amplification or mutation) with altered phenotype (38). These and other findings suggest that mutated p53 and other such genetic changes can appear early in multistep head and neck carcinogenesis (i.e., in histologically normal high-risk tissue) and may serve as useful biomarkers of cancer risk and of response in chemoprevention trials (4, 39).

**Clinical Trials**

Chemoprevention trials in the head and neck have been conducted in two major disease systems. The earliest trials were conducted in the treatment of oral leukoplakia, a premalignant lesion. Positive results in this disorder led to subsequent clinical trials in the related setting of preventing SPT after primary cure of head and neck cancer.

**Oral Premalignancy: Primary Chemoprevention.** Oral premalignant lesions are characterized clinically by white (leukoplakia) or red (erythroplasia) mucosal lesions in the oral cavity or oropharynx.
that cannot be scraped off or classified as any other disorder. These lesions are generally tobacco-related precursors of squamous cell carcinoma, are easily monitored, and have useful preclinical models. Oral premalignancy, therefore, is an excellent system for chemoprevention study because of its etiological, biological, and regional relationship through field carcinogenesis to aerodigestive tract cancers (39).

Surgical removal or laser excision are the standard therapies for patients with oral leukoplakia, but local treatment is often not useful in patients with extensive multiple lesions and does not treat the wide field of high-risk tissue (1, 2).

Several single-arm trials have suggested that various agents have activity against oral leukoplakia. These agents include β-carotene, vitamin E, and selenium (39, 40). Although all three agents have produced promising results, none has undergone randomized placebo-controlled testing to establish activity. The only class of agents that has emerged from single-arm testing into randomized trials is the retinoids (39, 41).

Five randomized studies of retinoids have been conducted in oral leukoplakia. In late 1982, we developed the first randomized chemoprevention trial of primary therapy in oral leukoplakia, a short-term, placebo-controlled, double-blinded study of high-dose 13cRA (1–2 mg/kg/day). The 44 participants in this study received treatment for 3 months, followed by 6 months of follow-up. We found that the retinoid treatment reversed leukoplakia lesions both clinically and histologically in over one-half of the treated patients. The clinical (complete-plus-partial) response rate was 67% (16 of 24) with 13cRA and 10% (2 of 20) with placebo (P = 0.0002). Dysplasia was reversed in 54% (13 of 24) who received 13cRA and 10% (2 of 20) who received placebo (P = 0.01). The toxicity of high-dose 13cRA was, however, unacceptable for use in the general population. Also, more than 50% of the responding patients relapsed within 2–3 months of treatment cessation (42).

This study established the short-term activity of high-dose 13cRA in inducing remission of oral leukoplakia and revealed that this therapy resulted in unacceptable toxic effects and a high relapse rate. These results led us to design and conduct the first randomized maintenance trial of less toxic therapy in patients with oral leukoplakia (43). This trial randomized patients whose lesions responded or remained stable following high-dose 13cRA induction therapy (1.5 mg/kg/day for 3 months). The study group was then randomly assigned to receive maintenance therapy with low-dose 13cRA (0.5 mg/kg/day) or β-carotene (30 mg/day) for 9 months.

A total of 70 patients were enrolled in this National Cancer Institute trial. Following the induction phase, the clinical response rate was 55%, which was consistent with the results of our earlier study; furthermore, the degree of dysplasia was reduced in 43% of patients. Following the maintenance phase, only 8% of the patients (2 of 24) in the low-dose 13cRA group progressed, whereas 55% (16 of 29) of patients in the β-carotene group progressed (P < 0.001). The rate of response to maintenance therapy beyond that achieved with high-dose induction therapy was also higher in the 13cRA group (33%) than in the β-carotene group (10%). Disappointingly, invasive or in situ carcinoma has developed in seven patients from the β-carotene group and in one patient from the low-dose 13cRA group. Furthermore, although the toxic effects in the maintenance phase were fairly mild, they were still significantly greater in the low-dose 13cRA group than in the β-carotene group. Adverse reactions in the low-dose 13cRA group included dry skin, cheilitis, conjunctivitis, and hypertriglyceridemia. Two subsequent randomized trials in leukoplakia are supportive of the retinoid activity achieved in our primary therapy trial. A placebo-controlled 6-month study of natural vitamin A by Stich et al. (44) achieved significantly higher complete remission rates and lower progression rates in the oral lesions of 54 Asian betel nut chewers. A 4-month placebo-controlled study by Han et al. (45) of a synthetic retinamide achieved significant primary clinical activity.

A recent interim analysis from an ongoing randomized maintenance trial is supportive of the results of our earlier maintenance trial. Under way in Italy, this trial is comparing the efficacy of a synthetic retinamide (fenretinide) in preventing relapse after excision of a lesions with the efficacy of no treatment. The current analysis of 71 evaluable patients indicates significantly lower relapse rates in the retinoid arm (46). Both our and the Italian trials are remarkably similar in having low retinoid-arm relapse rates, 8 and 7.7%, respectively, and in having significantly greater control-arm relapse rates, 55 and 29%, respectively.

Although five randomized trials have demonstrated significant activity of retinoids in reversing oral premalignancy, caution must be exercised before drawing overly optimistic conclusions from these results: (a) whereas the presence of oral leukoplakia is associated with an increased incidence of transformation to oral cancer, the reversal of these lesions has not been demonstrated to reduce the risk of developing cancer, the ultimate goal of chemoprevention; (b) there is no established optimal dose and schedule or specific retinoid for use in reversing oral premalignancy; (c) surgical or laser resection frequently is used successfully in the management of oral leukoplakia, and so further studies will have to assess when chemoprevention should replace or adjoin standard local therapy.

Work in the laboratory is keeping pace with the clinical trials in furthering the development of retinoids for chemoprevention. In 1987, two independent research groups discovered a nuclear retinoic acid receptor within the well-understood steroid receptor family (47). Intensive subsequent research discovered two distinct classes of retinoic acid receptors (RAR and RXR) and that these receptors may mediate the biological effects of retinoids by modulating gene transcription (48). Further in vitro and in vivo studies by Lotan et al. indicated that the expression of one RAR subtype, the β-receptor, is greatly reduced in late stage carcinogenesis of the head and neck (49). These researchers also observed that low expression of RAR-β in cancer cell lines could be up-regulated by the addition of a retinoid.

Lotan's group then conducted new studies to determine whether expression of RAR-β is also low in vivo in human oral premalignancy and whether retinoid therapy would affect RAR-β expression in these lesions (43, 49). They used in situ hybridization with antisense RNA to detect mRNA of RAR in biopsy specimens from premalignant oral lesions.

In accordance with the primary hypothesis, the pretherapy analyses by Lotan et al. indicated that RAR-β expression was below normal in premalignant lesions. Of the utmost importance was that the analyses conducted after therapy indicated that this expression increased significantly and correlated with lesion response to 3 months of induction with high-dose 13cRA. These results imply that the loss of expression of RAR-β is involved in the development of head and neck cancer and suggest the provocative possibility that retinoid chemopreventive activity in the UADT is related to up-regulation of RAR-β (4).

Oral premalignancy is a unique in vivo model system for the study of retinoid mechanisms of action: retinoid clinical-histological activity is established in this system, and tissue for mechanistic studies can be obtained from the oral cavity easily and virtually noninvasively (39). The RAR-β study by Lotan et al. and the related prospective clinical trials within this model system offer a paradigm of laboratory-clinical interaction in the field of chemoprevention. This interactive work illustrates the potential for making highly significant discoveries that could not be made by either clinical trials or laboratory cell line studies alone.

**Second Primary Tumors: Adjuvant Chemoprevention.** The rationale for using retinoids adjunctively to prevent the development of...
SPT is based on the field carcinogenic link of SPT to oral premalignancy (in which retinoids are highly active) and the high incidence and rate of mortality from SPT (39). Prospective SPT rates in head and neck cancer are approximately 5-7%/year; SPT are the major cancer-related cause of death in patients with early stage disease (3, 4). Local therapy (surgery or radiotherapy) does not address the field-wide carcinogenic process that can lead to the development of SPT throughout the aerodigestive tract. The integration of effective chemoprevention to follow curative primary therapy would address the serious problem of SPT development and would be a major advance in the control of head and neck cancers.

We prospectively studied 103 stage I-IV (M0) patients (50). After definitive treatment, these patients were randomized to receive either high-dose 13cRA or placebo for 12 months. The first 44 patients received 13cRA at a dose of 100 mg/m²/day. Because 13 of them required reduction to 50 mg/m²/day secondary to toxic effects, the protocol was revised for the remaining 59 patients, who were begun at a dose of 50 mg/m²/day. The major end points of this adjuvant trial were primary disease recurrence (local, regional, or distant) and the development of an SPT.

We found that 13cRA had no impact on primary disease recurrence. However, patients in the 13cRA group had significantly fewer SPT than patients in the placebo group, suggesting that in this setting, single-agent 13cRA is effective in suppressing or abrogating premalignant foci but cannot eliminate fully transformed cancer cells.

The initial report of this study, after a median follow-up of 32 months, indicated that high-dose 13cRA significantly reduced the rate of development of SPT (P = 0.005). The median follow-up is now 55 months (51). Two years after starting 13cRA, the protective retinoid effect on all SPT decreased, which suggests that the chemopreventive effect is reversible. Despite the fact that the annual overall SPT rates have evened out, the cumulative number of patients with SPT in the two arms remains different, although the difference is less significant than it was (P = 0.04). Subset analysis of only tobacco-related SPT rates indicates a persistent retinoid effect at the same level of statistical significance.

Reduced SPT rates notwithstanding, 13cRA did not significantly prolong survival over that in the placebo group. Several factors contributed to this: similar rates of primary disease recurrence (local, regional, or distant) in both arms; a high dropout rate related to toxic effects in the 13cRA arm; and prolonged survival in patients who develop SPT (which develop more frequently in the placebo group) due to early detection and therapy.

The higher rate of multiple SPT in the placebo-treated patients than the 13cRA group strongly supports the field carcinogenesis concept and the evidence of the systemic activity of 13cRA. Further clinical support of field carcinogenesis comes from the fact that over 80% of SPT of the squamous cell carcinoma histological type occurred within the carcinogen-exposed field at risk (head and neck, lung, or esophagus). There was no correlation between SPT rates and smoking status in the SPT analyses, the substantial toxicity-related noncompliance in the retinoid group underscore the significant results of adjuvant 13cRA.

These important findings are being extended in a large-scale trial of adjuvant chemoprevention in early stage head and neck cancer patients, in whom SPT are the major cancer threat to long-term survival. This comprehensive double-blinded, placebo-controlled, phase III trial differs in design from our first trial in two major regards. The current study includes only early stage head and neck cancer patients, who are at high risk of developing SPT. It also includes a lower dose of 13cRA which was determined from the activity and toxicity results from our recent randomized leukoplakia maintenance study (Fig. 4).

The applicability of these head and neck findings to other tobacco-related cancers is suggested by a recent report by Pastorino et al. (52, 53) of a randomized study of high-dose vitamin A adjuvant therapy in stage I non-small cell lung cancer. The lung findings are remarkably similar to those of the head and neck cancer study. In both studies, over 70% of SPT occurred in the tobacco-exposed field, and the time to development of a tobacco-related SPT was significantly longer in the retinoid arms. The rates of primary disease recurrence (local, regional, or distant) were not significantly different between the arms. Neither study was associated with prolongation of survival, however, which in part reflects effective surgical salvage of SPT in these prospectively followed patients. A United States intergroup trial using a design similar to that of the head and neck trial is testing the ability of low-dose 13cRA to prevent SPT in stage I non-small cell lung cancer (4).

The results of the lung and head and neck studies that used rigorous criteria applied to prospectively followed patients suggest that the problem of SPT in patients with head and neck or lung cancer may currently be underrated. Although the data are limited, it seems significant that prospective studies have reported SPT rates for head and neck and lung cancer that are roughly 2-fold higher than retrospective or tumor registry data (4).

Conclusion

The limited impact of standard therapy (chemotherapy, surgery, or radiotherapy) on survival, the morbidity resulting from surgical control, and the ominous threat of SPT faced by “cured” patients provide the impetus for the intensive ongoing efforts to establish greater control over head and neck cancer. Substantial progress has been made. Voice preservation has been achieved with primary chemoradiotherapy in most cases of locally advanced laryngeal cancer without compromising survival. Although voice preservation improves the quality of survival, survival itself in these cases has not been prolonged. Ongoing studies aimed at enhancing local-regional and distant control may translate into the ultimate goal of improved survival rates for head and neck cancer patients.

Chemoprevention research is producing promising results with the retinoid 13cRA in the UADT. The ability of 13cRA to reverse premalignancy and prevent SPT brings this chemopreventive agent to the threshold of becoming standard therapy for fieldwide multifocal disease. Before it can be accepted as a standard, however, this agent’s ultimate efficacy (i.e., impact on survival rates), toxicity, and integrative role with currently standard therapies will need to be resolved.

Fig. 4. Series of completed and ongoing randomized head and neck cancer chemoprevention trials at M. D. Anderson Cancer Center. NEJM, New England Journal of Medicine; NCI, National Cancer Institute.
Some of the most exciting new research in the head and neck is coming out of the laboratory. Recent molecular studies have detected specific genetic changes in specimens of high-risk UADT tissue that are histologically normal. These observations of genetic changes provide the strongest evidence supporting the concepts of multistep and field carcinogenesis and may cause premalignancy to be redefined in terms of molecular rather than clinical-histological criteria. Molecular biomarkers may serve ultimately as intermediate end points for chemoprevention trials (54).

Extremely valuable findings are coming from laboratory studies that are integrated within clinical trials. RAR-ß was identified by purely basic laboratory research; its expression was observed to be reduced in human head and neck cancer cell lines and tumor specimens. Later laboratory-clinical collaborative work confirmed that expression of RAR-ß is reduced in human premalignant tissue specimens. These observations of genetic changes provided an impetus for the development of RAR-ß as a potential biomarker for chemoprevention agents and their evaluation in animal models and human clinical trials: a review. Cancer Res., 52: 2-9, 1992.

The highly inventive and productive collaboration between laboratory and clinical researchers in cancers of the head and neck should hasten the achievement of better prevention and control of these cancers. This collaboration also may provide a paradigm for future study of cancers of other sites.

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References


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